ISSN: 0975 -8542

Journal of Global Pharma Technology

Available Online at: www.jgpt.co.in

RESEARCH ARTICLE

Food Poisoning and Its Prevention on the Example of Listeria Monocytogenes

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Abstract

Listeriosis is one of the most serious and severe foodborne diseases characterized by a high mortality rate of 20% to 44%. The purpose of the research is to study the age-related features of the clinical symptoms of listeriosis in adults, as well as the influence of comorbid conditions on its course. The study included 73 patients with listeriosis (43 (58.9%) men and 30 (41.1%) women; average age (48.83 ± 6.29) years). They were divided into 2 groups: group 1 (n = 29) - patients aged 18-49 years, group 2 (n = 44) - patients aged over 50 years. Septicemia is most common clinical syndrome in patients with listeriosis, presented in 46 (63%) patients. It's followed by damages of the central nervous system, namely meningitis and meningoencephalitis in 26 (35.6%) patients; gastroenteritis in 10 (13.7%) patients; and skin lesions in 3 (4.1%) patients. Septicemia was a typical clinical syndrome for patients over 50 years old - in 33 (75%) patients compering to 13 (44.8%) in the younger age group (OR = 3.69, 95% CI [1.36-10.04]). The damages of the central nervous system, namely meningitis and meningoencephalitis were typical for younger age group - 16 (55.2%) patients while 10 (22.7%) cases among the older age group (OR = 4.18, 95% CI [1, 51-11.56]). The mortality rate was 27.4% (of which 80% of deaths occurred in the older age group). Listeriosis is characterized by a severe course and a high mortality rate from septicemia and CNS damages. It is the cause of concomitant pathology development in immunocompromised individuals.

Keywords: *Adult listeriosis, Age-related features of listeriosis, mortality in listeriosis,* Comorbid *conditions and listeriosis, Prevention of listeriosis.*

Introduction

Food poisoning (FP) is among the most common cause of illness worldwide [1, 2]. FP affects one out of four Americans each year, and the annual cost of treatment is about 2-4 billion dollars [3]. Moreover, only 2.9% of patients seek medical treatment, the other part does not report about disease [4, 3]. The Foodborne Diseases Active Surveillance Network (Food Net) reported 25606 cases of FP in the United States, in 2018, where 5,893 patients were hospitalized and 120 died [5, 6].

FP has become a serious public health problem worldwide due to the increasing prevalence of morbidity and mortality in recent years and it causes widespread concern for consumers and food producers, trade organizations and regulatory authorities [7]. The clinical symptoms can be both general gastrointestinal symptoms (nausea, vomiting, abdominal pain, flatulence, diarrhea), and severe complications (sepsis, Reiter's syndrome, Guillain-Barré syndrome, death) [7, 1]. About 420,000 people die every year from FP and its complications, based the WHO researches [8]. Currently, about 250 FP pathogens are known, the prevalence of which has increased in recent years due to the globalization of the food market and changes in people diet [7]. Among the known bacteria that can cause a severe FP is Listeria *monocytogenes*, which is non-spore-forming gram-positive bacillus.

It is a facultative intracellular pathogen that causes listeriosis (L) (sporadic and epidemic) in humans and animals [9, 10]. L. *monocytogenes* is a cold-tolerant bacterium able to grow over a wide range of temperatures -0.4 ° C to + 45 ° C; adapted to high salinity (10% NaCl); survives at a pH value of 4.5- 9 [10]; and able to develop biofilms on the surfaces of production equipment, and therefore can live

on them for years [11]. This bacterium is quite common in the environment: in water, soil, and the intestines of animals [12, 13]. Vegetables can be contaminated with L. *monocytogenes* through the soil when using animal organic fertilizers and the infection of finished food products occurs during their processing [11, 12].

Researchers pointed out that products with long-term storage in fridge and products consumed without subsequent heat treatment are the most frequently contaminated with L. *monocytogenes* [8, 12]. Besides the alimentary route, transmission of L. *monocytogenes* is possible through inhalation of contaminated listeria dust, contact with a sick animal or carrier animal, the placental route from mother to child, or when the child passes through the birth canal [14].

There are two main types of listeriosis: a non-invasive and an invasive form. The non-invasive form develops quite rarely, mainly in healthy people, it's associated with foods products contaminated with a large amount of the pathogen; the clinically symptoms are fever, diarrhea, abdominal pain, myalgia, headaches, flatulence [14, 15]. The incubation period is from 2-3 days to 2 weeks. The small amount of L. *monocytogenes* does not develop the disease, while the consumption of a large amount of this pathogen with food leads to a weakening of the natural defense system of the gastrointestinal tract, liver and spleen, followed by the development of an invasive disease [16, 15].

An invasive form of the disease usually occurs in pregnant women, newborns, immunocompromised individuals and the elderly [15]. The morbidity of L is lower than other FP and ranges from 3 to 6 cases per 1,000,000 of the population worldwide [17, 18], however, a high mortality rate (20-44%) makes it one of the most dangerous FP [10].

Outbreaks of listeriosis occurs frequently throughout the world, and mainly in the spring and summer. In particular, the outbreak of L led to 37 deaths in Denmark, in 2014 [19], and to 1034 cases of the disease and 204 deaths in South Africa, in 2018 [20]. The frequency of L in the United States is about 0.3 cases per 100,000 people with 21% of deaths [6]. L. *monocytogenes* is the third most costly food pathogen after *Clostridium botulinum* and *Vibrio vulnifi cus*. In the USA, whose annual cost for the country's budget is from 2.3 to 22 billion dollars [17]. 567 cases of L occurred in China, from 2011 to 2017, with a mortality rate of 32.68% in the perinatal period and 23.78% in other age groups [18]. 759 cases of L were reported by another retrospective study conducted in China, between 2008 and 2017 (in 22 provinces of China), where 49% of the cases had clinical symptoms of sepsis, and 25% of central nervous system (CNS) damage, 18 % - deaths (of which 73% of deaths among newborns).

The peak incidence was in 2014, and the average age of patients among non-perinatal cases was 36 years, while 52% were men [10]. The listeriosis is quite difficult to treat that determines its severity and high mortality because. The main problem is that the intracellular nature of L. *monocytogenes* [17].

The studies have shown that lots of antibiotics are active in vitro against L. *monocytogenes*, however, in vitro studies cannot be always comparable with in vivo results, and most antibiotics show only a bacteriostatic effect on the listeriosis pathogen. Antibiotic, active against L. *monocytogenes*, should penetrate the host cell and firmly reach the intracellular target.

The drug should penetrate inside the cell and maintain a long-term optimal concentration in order to avoid the survival of the pathogen and the development of antibiotic resistance. Moreover, such an antibiotic must bind to penicillin-binding protein 3 (PBP-3) of Listeria, as this protein causes the death of the host cell. L. *monocytogenes* remains sensitive to all ß-lactam antibiotics except cephalosporins [14, 15]. Ampicillin is the drug of choice for treating L [21], however, the quite large dosage is required for achieving the bactericidal action. Studies have found that, the daily dose of ampicillin should be more than 9 g, and the duration of more than 21 days for the treatment of listeriosis meningitis in adults [22, 14].

However, the problem is that L often occurs in immunocompromised individuals whose defense mechanisms cannot eradicate the bacteria after a course of antibiotic therapy [14]. If a patient with an allergy to penicillin antibiotics is diagnosed with L, the vancomycin may be used until a culture and an antibiotic Gram study is obtained [15].

A combination of penicillin with aminoglycosides, fluoroquinolones and linezolid can also be used [22, 14]. The duration of treatment for invasive L has not been studied. Relapses are probably not so frequent; therefore 2-3 weeks of antibiotic therapy are sufficient. The severe course of rhombencephalitis with brainstem abscess requires a longer the course of treatment, however, there is no evidence confirming more than 4 weeks treatment [15].

The severe course of L, high mortality, a limited number of studies devoted to the clinical picture and treatment of the disease require a more in-depth study of the clinical features of this dangerous nosology, the development of effective treatment regimens, which will improve the prognosis and reduce mortality. The purpose of the research is to study the age-related features of the clinical symptoms of listeriosis in adults, as well as the influence of comorbid conditions on its course.

Material and Methods

The study included 73 patients with listeriosis (43 (58.9%) men and 30 (41.1%) women; average age (48.83 ± 6.29) years). To study the age-related features of the clinical symptoms of listeriosis, the patients were divided into 2 groups: group 1 (n = 29) - patients aged 18-49 years, group 2 (n = 44) - patients aged over 50 years. The study was conducted during 2016-2019. All participants signed an informed consent to participate in the study. The study was carried out in accordance with the "Ethical Principles for Medical Research Involving Human Subjects", approved by the Helsinki Declaration (1964-2013), Council of Europe Convention on Human Rights and Biomedicine (04.04. 1997), principles of ICH GCP (1996), EU Council Directive No. 609 (11.24.1986).

A diagnosis of L was made on patient complaints, an anamnesis of the disease, physical examination and mandatory bacteriological examination (depending on the form of the disease, the materials taken were blood, cerebrospinal fluid, feces, smear from the throat), carried out according to the standard method. The meat-peptone liver agar with glucose 0.5% and glycerol 2% was used as a nutrient medium. Antimicrobial susceptibility testing was also mandatory carried out.

The history of the disease was collected in great detail in order to determine the possible path and source of infection. All patients underwent a general clinical analysis of blood and urine, a study of the main biochemical parameters of blood (glucose, urea, creatinine, bilirubin and its fractions, thymol test, activity of alanine and aspartate aminotransferase, alkaline phosphatase, γ-glutamyl transferase, lactate dehydrogenase as well as coagulation test, ionogram, proteinogram), chest x-ray, electrocardiography, ultrasound of the abdominal organs, and in case of neurolisteriosis-spinal puncture.

Inclusion criteria: diagnosis of listeriosis confirmed by bacteriological method; the patient's age is over 18 years; the patient signed informed consent to participate in the study (in case of incapability, an informed consent was signed by the patient's first-line relative). The study did not involve underage patients, as well as pregnant, patients with neonatal listeriosis and mental disorders.

Statistical processing of the obtained data was carried out according to the Wilcoxon T and U criteria using the SPSS 13.0 software package and Microsoft Excel 2013 (Microsoft, USA). Differences were considered statistically significant at $p < 0.05$. Past3 program was used for comparing qualitative results between groups.

The Results of the Study

Analyzing the clinical symptoms of listeriosis in adults, septicemia was found as the most common, presented in 46 (63%) patients. It's followed by damages of the central nervous system, namely meningitis and meningoencephalitis in 26 (35.6%) patients; gastroenteritis in 10 (13.7%) patients; and skin lesions in 3 (4.1%) patients.

Analyzing the age-related features of the disease, certain differences were found in the frequency of manifestations of the main clinical syndromes listeriosis (Table 1). Particularly, septicemia was typical clinical syndrome for patients over 50 years old - in 33 (75%) patients compering to 13 (44.8%) in the younger age group (OR = 3.69, 95% CI [1.36-10.04]) with a statistically significant difference ($p < 0.05$). Damages of the central nervous system, namely meningitis and meningoencephalitis were typical for younger

age group - 16 (55.2%) patients while 10 (22.7%) among the older age group (OR = 4.18, 95% CI [1, 51-11.56]) with a statistically significant difference (p <0.05). The febrile gastroenteritis and skin lesions were found in patients of both groups with significantly less and approximately the same frequency (Table 1). Moreover, 4 (13.8%) people in group 1 had a combination of septicemia and central nervous system damage (meningitis, meningoencephalitis), the same was in 3 (6.8%) people of group 2; a combination of septicemia and febrile gastroenteritis was in one patient of each group. One (3.4%) patient of group 1 had a combination of septicemia, CNS damage and febrile gastroenteritis, and one (3.4%) patient had a combination of CNS damage and febrile gastroenteritis; one (2.3%) patient from group 2 had a combination of septicemia and skin lesions. Thus, 7 (24.1%) people in group 1 had an isolated form of septicemia, while 28 (63.6%) in group 2 (OR = 5.50, 95% CI [1.93-15.70]); an isolated damage to the CNS was in 11 (37.9%) people of the group 1 and 7 (15.9%) people of the group 2(OR = 3.23, 95% CI [1.07-9.73]); febrile gastroenteritis - 3 patients in each group (OR = 1.58, 95% CI [0.29-8.41]); skin lesions - 1 patient in each group (OR = 1.54, 95% CI [0.09-25.57]).

Table 1: Frequency of the main clinical syndromes of listeriosis depending on the age of the patients

Clinical symptoms	Study groups				OR	95% CI
	Group 1, 18-49 year (n=29)		Group 2, over 50 years (n=44)			
	Tot.	%	Tot.	%		
Septicemia	13	44.8	33	75	3.69*	1.36-10.04
CNS damages (meningitis, meningoencephalitis)	16	55.2	10	22.7	4.18*	1.51-11.56
Febrile gastroenteritis	6	20.6	4	9.1	3.47	0.79-15.25
Skin lesions	1	3.4	2	4.5	0.75	0.06-8.67
Note: * - the difference is statistically significant between the age groups of 18-49 years and over 50 years (p <0.05).						

The main clinical symptoms are febrile fever - in 62 (84.93%) people, headache - in 40 (67.12%) people, impaired consciousness - in 36 people (49.3%), myalgia - in 35 (47.95%) people, diarrhea - in 28 people (38.36%), abdominal pain - in 20 (27.4%) people (Fig. 1).

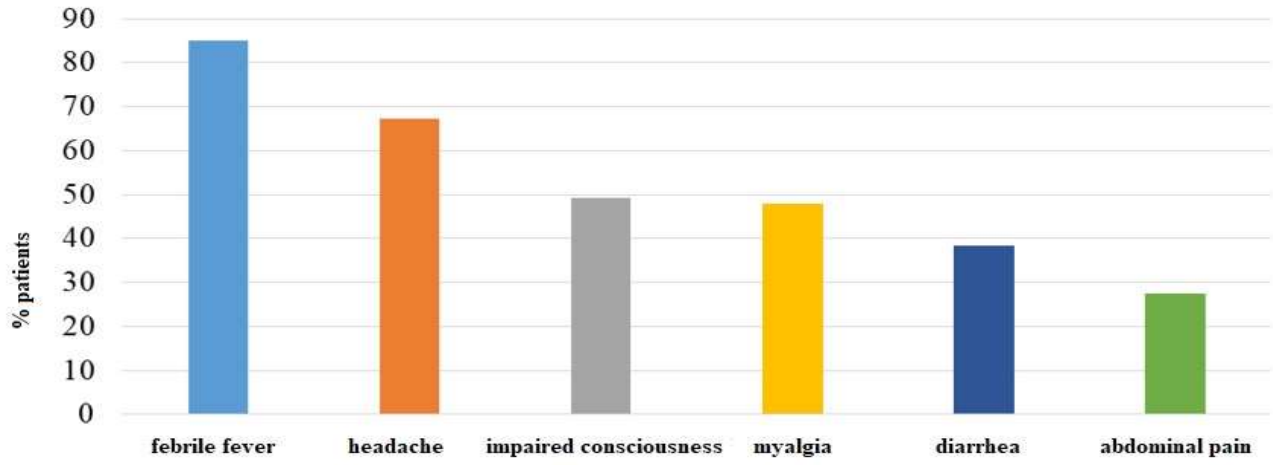

Figure 1: The frequency of the main symptoms in patients with listeriosis, %

Analyzing the concomitant pathology among the examined patients, 13 (44.8%) patients of the group 1 had one concomitant disease, 7 (24.2%) patients - two concomitant diseases, 4 patients (13.8%) - three concomitant diseases, 5 (17.2%) patients had no comorbid pathology; 10 (29.5%) patients in group 2 had one concomitant disease, 18 (40.9%) patients - two concomitant diseases, 9 (20.5%) patients - three or more concomitant diseases, 4 (9.1 %) patients had no comorbid pathology. According to the structure of the concomitant pathology, immunosuppressive conditions (including as a result of corticosteroids and

immunosuppressant intake) were present in 13 (44.8%) people (1 of them had AIDS), cardiovascular pathology - in 9 (31%) people, oncopathology - in 8 (27.6%) people, liver diseases - in 5 (17.2%) people, diabetes mellitus - in 4 (13.8%) people in the group 1; while cardiovascular pathology in 32 (72.7%) people, immunosuppressive conditions (including as a result of corticosteroids and immunosuppressant's intake) in 18 (40.9%) people, oncopathology in 14 (31.8%)) people, diabetes - in 8 (18 2%) people, liver disease - in 5 (11.4%) people, other diseases - in 4 (9.1%) people in the group 2.

The mortality was significantly higher in people of the older age group ($p < 0.05$). Thus, in group 2, mortality was 36.4% (16 people) of the total number of patients and 13.8% (4 people) in group 1 (OR = 3.57, 95% CI [1.05-12.11]). Generally, the mortality was 27.4% (20 people) among all participants. Meanwhile, the majority of deaths in group 2 were among people over 65 years old, 10 people (62.5% of all deaths in the group).

Among the four dead patients of group 1, three (75%) had a combination of septicemia and meningoencephalitis / meningitis, and 1 (24%) had septicemia, meningoencephalitis and febrile gastroenteritis. Among 16 dead patients of group 2 deaths, 9 (56.25%) patients had septicemia, three (18.75%) meningoencephalitis / meningitis, three (18.75%) combined septicemia and meningoencephalitis / meningitis, one (6.25%)) - a combination of septicemia and febrile gastroenteritis.

It should be noted that among 4 deaths of group 1, two (50%) patients had concomitant oncopathology with an immunosuppressive state, one (25%) patient had oncopathology with immunosuppressive state and diabetes mellitus, and one (25%) patient had AIDS. Among the deaths of the 2nd group, 5 (31.25%) people had a combination of oncopathology, an immunosuppressive state and cardiovascular disease, three (18.75%)- an immunosuppressive state and cardiovascular disease, three (18.75%)- oncopathology and cardiovascular disease, three (18.75%)- oncopathology, immunosuppressive state and diabetes mellitus, two (12.5%)- oncopathology, immunompressive state, cardiovascular disease and liver disease. According to the anamnesis collected, the disease was associated with the consumption of insufficiently thermally processed meat - 22 (30.1%) patients, milk - 17 (23.3%) patients, canned meat - 13 (17.8%)) patients, cottage cheese - 8 (11%) patients, processing of animal raw materials - 6 (8.2%) patients, prepared salads - 5 (6.9%) patients, seafood - 2 (2.7%) patients.

Discussion

According to the study results, L is not characterized by typical clinical symptoms inherent only to this disease, but non-specific symptoms as fever, myalgia, headache, diarrhea, general weakness. L is characterized by a severe course and it's the cause of concomitant pathology development in immunocompromised individuals (immunosuppressive conditions, oncopathology, cardiovascular diseases, diabetes mellitus, liver damage, etc.).

Septicemia and CNS damages, namely meningitis and meningoencephalitis were frequent clinical syndromes in the examined patients with L. Bacteremia at the beginning of the disease progression was like a flu (febrile fever, headache, myalgia, body aches) and / or diarrhea. CNS damage (neurolisteriosis) was characterized by neck stiffness or classic symptom triad of stiff neck, fever and impaired consciousness, in addition, some patients suffered from convulsions of varying intensity and amplitude.

Meanwhile, focal neurological deficit was present only in 15 (20.5%) patients, which is much less common compering to pneumococcal meningitis. The age-related differences in the frequency of septicemia and neurolisteriosis were found.

Thus, neurolisteriosis mostly occurred among people under 50 years, while septicemia in elderly patients. Mortality in the study was 27.4%, while 80% of deaths occurred in the older age group. It is explained by the more difficult somatic state of patients due to a greater number of comorbid pathology (diseases of the cardiovascular system, immunity pathology, cancer, diabetes, hepatitis, etc.), which significantly worsens the course and prognosis of the disease.

Therefore, patient's age, the cardiovascular diseases, malignant neoplasms, immunosuppressive conditions, diabetes, liver diseases are independent risk factors of L.

The data obtained on the main clinical symptoms of L are consonant with other studies that have been carried out in this field [23, 18, 10].For example, an English study from 2006 to 2015 [23] analyzing of laboratory-confirmed cases (1357 in total) of L, except for pregnant women, showed that the most common clinical symptom of L was also septicemia, which occurred in 943 (69.5%) patients.

It's followed by CNS damages, namely meningitis and meningoencephalitis in 304 (22.4%) patients, febrile gastroenteritis in 156 (11.5%) patients, others clinical symptoms - in 203 (15%) patients. Meanwhile, combined CNS damage with septicemia occurred in 162 (11.9%) patients, septicemia with febrile gastroenteritis in 103 (7.5%) patients, septicemia with other clinical manifestations in 72 (5, 3%), and CNS damage, septicemia, and febrile gastroenteritis occurred in 6 (0.4%) cases.

A frequent symptom of L was fever - in 832 (61.3%) people, impaired consciousness - in 517 (38.1%) people, diarrhea - in 475 (35%) people, headache - in 434 (32%) people, as well as abdominal pain - in 368 (27.1%) people. Mortality was 28.7%. According to the study, CNS damages were associated with a younger age (less than 50 years), and septicemia with older age (over 50 years). Moreover, independent risk factors are age over 80 years (OR = 3.32, 95% CI [1.92-5.74]), malignant neoplasms (OR = 3.42, 95% CI) [2.29-5.11]), cardiovascular diseases (OR = 3.30, 95% CI [1.64-6.63]), immunosuppressive conditions (OR = 2.12, 95% CI [1.40 -3.21]), liver disease (OR = 4.61, 95% CI [2.47-8.61]) (Scobie et al., 2019).

The Spanish retrospective analysis of 5696 cases of L from 1997 to 2015, showed that the prevalence of septicemia and meningitis / meningoencephalitis in the clinical symptoms, and men more often had meningoencephalitis comparing to women (47.4% and 37.3% (p <0.01), However, there were no statistically significant differences between males and females in case of septicemia (p> 0.05).

The sample of Spanish study predominated by patients older than 65, however, meningoencephalitis was also more frequent for the younger age group (45-64 years), while septicemia in people over 65. Mortality was 17% (death rate among people over 65 was 67.5%), which is significantly less than in our study: 56.4% of patients from the Spanish study had immunodeficiency, 22.8% - cancer, 16.6% - diabetes, 13.1% - chronic liver disease, that is comparable with our results [24]. Unlike the Spanish study, there was no statistically significant difference (p> 0.05) in case of meningoencephalitis between men and women in our study, which is probably due to a significantly smaller sample.

Similar data on the prevalence and characteristics of L were obtained in China during 2008 to 2017 [10]. An analysis of outbreaks reports between 2007-2015 in different countries and associated food products was conducted by Camargo et al [16]. The analysis showed that most often with outbreaks of L are associated with the consumption of semi-raw meat, prepacks, prepared salads, milk, soft cheeses, and seafood [16].

The results of our study are consistent with these data, however, in a relatively few people (only 2.7%) from our study listeriosis was associated with consumption of seafood, since seafood is not as popular as in countries Asia, Europe and USA [16, 25]. Analyzing the main ways of spreading and the data on the food products contaminated with this pathogen, that are the main factor in the transmission in the study, the following measures were established to reduce the amount of the pathogen in the environment: strict sanitary and epidemiological control of livestock facilities, enterprises for the production of meat, dairy and other food products in order to control the prevalence of L. *monocytogenes* on food products, raw materials, work surfaces.

Moreover, in case of an outbreak of disease, the indispensable identification of a food product transmitting the pathogen is required. For individual prevention of the disease (especially for people at risk), it is necessary to conduct sufficient heat treatment of meat and dairy products, seafood, avoid the use of convenience foods and prepared salads, as well as observing hand hygiene before and after processing food products of animal origin and animal raw materials.

Conclusions

Thus, listeriosis is characterized by a severe course and it's the cause of concomitant pathology development in immunocompromised individuals. The most common clinical syndrome was septicemia, which was present in 46 (63%) patients. It's followed by damages of the central nervous system, namely meningitis and meningoencephalitis in 26 (35.6%) patients; gastroenteritis in 10 (13.7%) patients; and skin lesions in 3 (4.1%) patients. Listeriosis is characterized by age-related differences in the frequency of manifestations.

The main clinical syndromes for patients over 50 years old was septicemia cooccurring in 33 (75%) patients compering to 13 (44.8%) in the younger age group (OR = 3.69, 95% CI [1.36-10.04]). Damages of the central nervous system, namely meningitis and meningoencephalitis were typical for younger age group - 16 (55.2%) patients while 10 (22.7%) among the older age group (OR = 4.18, 95% CI [1, 51-11.56]). Listeriosis is characterized by a high mortality rate - 27.4% (of which 80% of deaths occur in the older age category). The patient's age, the cardiovascular diseases, malignant neoplasms, immunosuppressive conditions, diabetes, liver diseases are independent risk factors for L.

Prospect for further research is the study of the clinical features of neonatal listeriosis and the development of effective antibiotic therapy regimens that will improve the prognosis and reduce the mortality rate among newborns.

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